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Azzeri, Amirah; Shabaruddin, Fatiha Hana; Tan, Soek-Siam; Dahlui, Maznah; McDonald, Scott A.; Kamarulzaman, Adeeba; Mohamed, Rosmawati

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Amirah Azzeri (1), Fatiha Hana Shabaruddin (2), Soek-Siam Tan (3), Maznah Dahlui (4),(5), Scott A McDonald (6),(7), Adeeba Kamarulzaman (8) and Rosmawati Mohamed (9)

1 Department of Social and Preventive Medicine

2 Department of Pharmacy, Faculty of Medicine, University of Malaya, Kuala Lumpur

3 Department of Hepatology, Selayang Hospital, Selangor

4 Centre of Population Health, Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

5 Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia

6 Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, The Netherlands

7 School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, Scotland

8 Centre of Excellence for Research in AIDS

9 Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

ABSTRACT

Chronic hepatitis C virus (HCV) infection is often asymptomatic until an occurrence of severe liver disease. A descriptive cross-sectional study was conducted of a hospital-based case-series in 2014 on 741 consecutive HCV patients presented at the national referral center in Malaysia, a middle-income Southeast Asian country. Mean age at initial presentation was 48 years (SD =11.5; median = 49) with 541 (73%) males. Prior known exposure to HCV risk factors were intravenous drug use (n = 271/737) and blood product transfusion (n = 237/737). HCV-genotype distributions were G3 (37.1%), G1 (21.4%), G2 (0.3%), G4 (0.1%) and G6 (0.1%), with 41.0% untested. Cirrhosis and non-cirrhotic chronic infection was present in 44 [mean (SD) age = 52 (9) years and 56% (mean (SD) age = 44 (12) years] patients, respectively. Of the 327 cirrhotic patients, 36% and 14% had decompensated cirrhosis and hepatocellular carcinoma respectively. Eighty percent patients were eligible for interferon treatment based on their stage of liver disease, but only 50% of the eligible patients received the treatment. Thus, HCV-infected patients at initial presentation to a tertiary care center in Malaysia reflected delayed presentation with a disproportionately high number of patients with liver cirrhotic. Improving access to clinical care and optimizing treatment with direct acting antiviral drug is essential to reduce the country's burden of hepatitis C.

Keywords: cirrhosis, epidemiology, hepatitis C, middle-income Malaysia country

INTRODUCTION

Globally, 64-103 million people are chronically infected with hepatitis C virus (HCV), while viremia prevalence among adults in Asia Pacific countries is 0.4-1.1% (Gower et al, 2014). In Malaysia, 2.5% of the population 15-64 years of age is estimated to be anti-HCV-positive in 2015 and the total adult population with chronic HCV infection estimated at 368,500 (McDonald et al, 2014). Worldwide genotype 1 accounts for 50% of hepatitis C cases followed by genotype 3 (28.6%) (Messina et al, 2015). In Malaysia, the predominant HCV genotype is genotype 3 followed by genotype 1 (Mohamed et al, 2013; Ho et al, 2015).

Generally, 35% of individuals with acute hepatitis C achieve spontaneous viral clearance within two years postinfection, while the remaining progress to chronic HCV infection (Micallef et al, 2006). Among the chronically-infected patients, approximately 20% will develop liver cirrhosis within 20-30 years (Westbrook and Dusheiko, 2014), which can lead to hepatic decompensation, hepatocellular carcinoma (HCC) and death, with hepatitis C being the leading cause of HCC and liver transplantations worldwide (Kim and Chang, 2013). Following the onset of cirrhosis, the annual risk of developing decompensated cirrhosis (DC) and HCC is 3-6% and 1-5%, respectively (Maasoumy and Wedemeyer, 2012; Westbrook and Dusheiko, 2014). For patients with DC, the annual mortality risk is 15–20% (Westbrook and Dusheiko, 2014).

Asymptomatic presentation of early hepatitis C infection often leads to many infected individuals being unaware of their infected state (Gupta et al, 2015; Zhou et al, 2015; Alejandro et al, 2016). Patients commonly are admitted into clinical care after developing clinical sequelae, which are usually irreversible and associated with high morbidity and mortality (Degos et al, 2000). The World Health Organization (WHO) recommends direct acting antiviral (DAA) regimen, such as sofosbuvir + velpatasvir, ledipasvir + sofosbuvir and ombitasvir + paritaprevir + ritonavir, as the current drug of choice for treatment of hepatitis C in place of the traditional subcutaneous interferon-based (IFN) therapy (WHO, 2017).

WHO has also established the Global Health Sector Strategy 2016-2021 on viral hepatitis, which recommends all countries to aim for the elimination of viral hepatitis by 2030 (WHO, 2016). In order to develop national policies and strategies to achieve this goal, there is a need to identify hepatitis C-infected population presenting at a local clinical care center to provide accurate information for the development of national policies for treatment and control of hepatitis C infection.

Hence, this study describes the clinical characteristics and disease stages of chronic HCV-infected patients during initial presentations at the main national tertiary-care referral center in Malaysia.

MATERIALS AND METHODS

Study location and population

A descriptive cross-sectional analysis was conducted of a hospital-based caseseries on consecutive HCV patients who presented in 2014 at the national tertiarycare referral center. Selayang Hospital, located in Klang valley, an area with the highest population density in the country (Department of Statistics Malaysia, 2010), is a public healthcare institution and the main tertiary-care referral center for liver diseases in Malaysia. The Hospital has the largest number of hepatologists and gastroenterologists among public healthcare institutions and receives referrals for liver cases from all over Malaysia (Hospital Selayang, 2014).

Data on socio-demographic background and clinical characteristics of patients with chronic HCV were collected from Selayang Hospital medical record database from their initial presentation until the end

of 2014. Results on HCV viral loads, genotypes and subtypes tests were collected as available in the database.

Chronic HCV patients were classified into cirrhotic and non-cirrhotic types. Cirrhotic patients fulfilled the following criteria: (i) modified histologic activity index score of 6 based on liver biopsy results, and/or (ii) METAVIR score of F4 based on fibroscan result, and/or (iii) aspartate aminotransferase-to-platelet ratio index (APRI) score ≥2 (Castéra et al, 2005). HCV patients were further classified into compensated and decompensated cirrhosis, with or without HCC. Severity of cirrhosis was graded using the Child-Pugh (CP) classification (Khullar et al, 2015). HCC was diagnosed mainly through dynamic imaging studies (multiphasic CT scan or MRI) or liver biopsy, with or without raised alpha-fetoprotein levels (Galle et al, 2018).

The study received ethics approval from the National Medical Research Registry and Ethics Committee of Malaysia (NMRR-15-1559-27223).

Laboratory assays

Identification of viral load and genotype (with or without subtype) was conducted using qualitative and quantitative tests for detection of HCV RNA (reverse transcription and PCR-based amplification) and nucleic acid sequencing, respectively (Mohamed et al, 2013; Ho et al, 2015). The latter results were compared with sequence information (genotype patterns) deposited at GenBank, and, in some cases, phylogenetic analysis was conducted to specify subtypes of the detected genotype (Mohamed et al, 2013; Ho et al, 2015).

Data analysis

Data analysis was conducted using SPSS version 22.0 (IBM, Armonk, NY).

RESULTS

There were 741/5,865 (12.6%) patients with active hepatitis C infection treated by the Hepatology Department, Selayang Hospital, Klang valley, Malaysia in 2014. Data were collected for all 741 patients from their first visit to the Hepatology Department until the end of 2014. Of the patients included in this study, 541 (73.0%) were male with mean (SD) age at initial presentation was 48 (11) years (median = 49). The most common age group at initial presentation was 50-59 years (n = 255, 34.4%), followed by 40-49 years (n = 225, 0.4%). Prior known exposure to HCV risk factors obtained from available data for 737 patients were (in decreasing order of frequency) intravenous drug use (IVDU) (n = 271, 36.8%), history of blood or blood products transfusion (n = 237, 32.2%), having multiple sexual partners (n = 123, 16.7%), tattooing, cupping therapy, acupuncture and/or sharing of personal sharp items with infected individuals (n = 68, 9.2%), history of dialysis (n = 38, 5.2%), and recipient of organ transplantation (n = 13, 1.8%), with some patients having been exposed to multiple HCV risk factors.

Of the 741 patients, 631 and 535 patients were tested for hepatitis B surface antigen (HBsAg) and HIV antibodies, resulting in 34 (5.4%) and 51 (9.5%) patients, respectively being positive. Four (0.5%) patients had triple infections (HCV, hepatitis B and HIV).

Median (range) baseline HCV load was 3.1x106 (64 - 861.3x106) copies/ml, with high baseline viral load (>6 x106 copies/ ml) in 33.3% of chronic HCV patients. Of the 437 patients tested for HCV genotype, genotype 3 was the most common (n = 275, 63.0%) followed by genotype 1 (n = 158, 36.1%), genotype 2 (n = 2, 0.5%), genotype 4 (n = 1, 0.2%), and genotype 6 (n = 1, 0.2%). Subtypes data were available for 243/275 genotype 3 and 140/158 genotype 1 patients, respectively. Numbers

of patients with genotype 3a and 3b were 236 (97%) and 7 (3%), respectively, and with genotype 1a, 1b and 1a/1b were 87 (62%), 49 (35%) and 4 (3%).

At initial presentation, 414 (56%) and 327 (44%) patients were non-cirrhotic [mean (SD) age = 44 (12); median = 45] and cirrhotic [mean (SD) age = 52 (9) years; median = 52 years]. The majority of cirrhotic patients (267, 82%) were <60 years of age and 209 (64%) had compensated cirrhosis [mean (SD) age = 53 (9); years; median = 52 years] while the remaining (36%) had decompensated cirrhosis [mean (SD) age = 52 (9) years; median = 52 years] (Table 1).

The 118 decompensated cirrhosis patients were further categorized according to CP classification, with 92 (78%) and 26 (22%) patients in CP(B) and CP(C), respectively, while 69 (58%), 62 (45%) and 12 (10%) patients had variceal bleeding, ascites and hepatic encephalopathy, respectively. Of the 327 cirrhotic hepatitis C patients, 45 (14%) had HCC, with 28 (62%), 14 (31%) and 3 (7%) in CP(A), CP(B) and 3/45 CP(C) category, respectively.

All patients with non-cirrhotic chronic infection and compensated cirrhosis (595/741, 80.3%) were considered clinically eligible for IFN therapy, assuming no other restricting factors for treatment initiation such as comorbidities, refusal and loss to follow-ups. Overall, 123 (20.7%) patients achieved sustained virologic response (SVR) following IFN therapy, among whom 99 (80%) and 24 (20%) were non-cirrhotic and compensated cirrhotic respectively, with 83, 39 and 1 having HCV genotype 3, 1 and 2 infection, respectively.

There were 262/741 (35%) patients who received treatment for HCV infection, 255 (97%) with IFN-only treatment, 5 (2%) with both IFN and DAA and 2 (1%) with DAA drugs . Among the five patients who received both IFN and DAA, two received IFN, ribavirin and boceprevir for 48-weeks while three patients initially received IFN-based treatment and were subsequently treated with combination regimens of sofosbuvir, daclatasvir and ribavirin for 24 weeks, ombitasvir, paritaprevir, ritonavir, dasabuvir and ribavirin for 24 weeks and grazoprevir and elbasvir for 12 weeks, respectively. Among the two treatment-naïve patients who received DAA, both were treated with a combination regimen of ombitasvir, paritaprevir, ritonavir, dasabuvir and ribavirin for 12 weeks. All seven patients who received DAA had HCV genotype 1 infection without cirrhosis.

Among all patients, 479 (64.6%) had viremia but did not receive treatment for HCV infection for the following reasons: (i) ineligible for IFN treatment due to DC and HCC (n = 146; 30%), (ii) refused treatment (n = 89, 19%), (iii) ineligible for IFN treatment due to such factors as comorbidity, old age or active IVDU (n = 85, 18%), and (iv) loss to follow-up (n = 79, 16%). The remaining (17%) patients who did not receive treatment because of failure to respond to previous IFN treatment, chose to be treated at other institutions or were awaiting a more affordable DAA.

Table 1 - Stages of liver disease at initial presentation of hepatitis C virus -infected patients according to age groups at the national tertiary-care referral center, Malaysia during 2014.

	Stage of liver disease Number of patients		
	Non-cirrhotic	*Compensated cirrhosis*	*Decompensated cirrhosis*
Age group (years)			
≤39 (*n* = 165)	140	15	10
40-49 (*n* = 225)	133	55	37
50-59 (*n* = 255)	105	96	54
≥60 (*n* = 96)	36	43	17
Total	***414***	***209***	***118***

DISCUSSION

To the best of our knowledge, this is the first and largest study to describe clinical characteristics and disease stages of chronic HCV-infected patients at initial presentation at tertiary care center in Malaysia. Almost 50% of the hepatitis C patients at the referral center presented with liver cirrhosis, similar to findings from other middle-income countries (de Oliveira et al, 2014; Gupta et al, 2015).

Based on the European Association for the Study of the Liver (EASL) definition (EASL, 2015), patients who present with significant fibrosis without previous antiviral treatment are considered as delayed presentation of chronic hepatitis C. In this study, 72% of the patients were in this category mainly due to unawareness of their hepatitis C status owing to the subclinical manifestations at early stage of infection; approximately 75-80% of HCV infected individuals are asymptomatic and only become aware of the infection after serological testing is conducted (Zhou et al, 2015). This delayed presentation is particularly of concern among Asian hepatitis C patients, who have no clear risk factors for HCV acquisition compared to other ethnicities, such as Caucasians and Hispanics, but in fact are at risk due to such common practices in Asian countries as acupuncture, sharing shaving kit and use of roadside barber (Nguyen and Nguyen, 2013). These common practices make a risk-based screening strategy challenging as it becomes difficult to identify a high-risk group among the general population, besides the obvious high-risk population of IVDU and those with a history of blood transfusion (Nguyen and Nguyen, 2013; Suthar and Harris, 2015).

The time lag from HCV diagnosis to tertiary care referral is also an important factor in the delayed presentation for clinical management of HCV patients (Yau et al, 2015). In Malaysia, there is a paucity of data on referral rate or time between diagnosis of hepatitis C at a primary care center and presentation at a tertiary care institution, with an estimated referral rate (from primary care to hepatology or gastroenterology specialist care) of 13% in 2016 in 10 of 12 states in Malaysia, the main reason being patient's refusal of IFN therapy, which was previously the main option for HCV treatment before the introduction of DAA drugs within the national public health care system (Ali N, personal communication). Malaysia is an example of a middle-income Asian country that recently (in 2018) has DAA drugs available in the national public healthcare system as the main treatment option for HCV disease, and thus, the treatment rate presented in this study mainly reflected previous use of IFN therapy.

Delayed presentation at advanced stage of liver disease has significant impact on (i) HCV-infected individual in term of lower success rate of treatment (The American Association for the Study of Liver Diseases and Infectious Diseases Society of America, 2017), (ii) healthcare system with regards to higher healthcare utilizations and healthcare costs for disease management (Razavi et al, 2013; Myers et al, 2014; Azzeri et al, 2017), and (iii) society at large due to risk of transmission of an on-going disease in the general population (Hickman et al, 2015).

Globally, DAA drugs are now widely used for the treatment of HCV infection. The predominant HCV genotypes in Malaysia are genotype 3 followed by genotype 1, accounting for 99% of all HCV cases (Mohamed et al, 2013; Ho et al, 2015). This implies that any DAA regimen with proven efficacy for these two genotypes could be adopted within a simple management protocol. Standard use of such DAA regimens for all non-cirrhotic and cirrhotic patients would remove the need for genotyping and thus will further expedite initiation of treatment for all HCV infected patients. Hypothetically, if DAA is available as standard HCV treatment for this study population (as compared to the previously use of IFN), the proportion of patients who would be eligible for HCV treatment will rise to 94% compared to 80% due to the wider eligibility for DAA treatment for patients, including those with decompensated cirrhosis, assuming no other restricting factors for treatment initiation, such as comorbidity, refusal and loss of follow-up.

However, HCV-infected patients with advanced liver disease have been known to achieve lower SVR rates with DAA compared to patients without cirrhosis or with compensated cirrhosis (Curry et al, 2015; Foster et al, 2015). There also is evidence indicating improvements in the symptoms of liver disease after treatment with DAA among patients with decompensated cirrhosis, while CP(C) is not sufficient in preventing the need for liver transplantation or mortality (The American Association for the Study of Liver Diseases and Infectious Diseases Society of America, 2017). This highlights the importance of early presentation for initiation of treatment at the early stages of liver disease among HCV patients.

This study finds, at initial presentation at a tertiary care center, cirrhotic patients were relatively young and the majority of patients with cirrhosis (with or without HCC) were less than 60 years of age. Development of liver cirrhosis among relatively young HCV-infected patients may reflect use of illicit drugs before 20 years of age (Novick et al, 1985), which represents the biggest risk factor for HCV transmission in Malaysia (Vicknasingam et al, 2009) with liver cirrhosis developing 25 to 30 years following initial exposure to infection (Thein et al, 2008).

Several other factors may contribute to the observation of liver cirrhosis at a young age in this study cohort. The majority of the patients were male and infected with HCV genotype 3, factors associated with rapid fibrosis progression in hepatitis C disease (Maasoumy and Wedemeyer, 2012; Toshikuni et al, 2014; Lingala and Ghany, 2015). Development of cirrhosis at a relatively young age has also been observed in other studies (Sajja et al, 2014; Silva et al, 2015; McDonald et al, 2017). The development of liver cirrhosis among relatively young patients who are in the working-age group may lead to financial problems to the patients and their families due to loss of income, lower productivity and significant time and costs for treatment (Federico et al, 2012; Scalone et al, 2015). Patients in this group are potential breadwinners of the family and hepatitis C disease can cause them to be less economically productive owing to reduced ability to work and potential job loss from illness (Scalone et al, 2015). Cirrhotic patients spend 7% of their annual income for clinical treatment and have significant time loss from work due hospitalization and visits to clinics (Federico et al, 2012).

However, the findings of this study must be interpreted with caution. The use of a retrospective hospital database may have led to variations in the availability of patients' information from medical records, which in turn could have resulted in missing such data as baseline viral load, virus genotypes, risk factors and SVR achievement rates. In order to minimize this inherent weakness, relevant data (as much as possible) were requested from other available records within the hospitals. As this study was conducted at a national tertiary care referral center, the distribution of disease stages could potentially be disproportionate towards the more severe stages (referral bias). In addition, while the number of patients in the present study is small, the sparse available evidence suggests only a small proportion of symptomatic HCV patients were in tertiary care, possibly due to the low referral rate and the previous lack of treatment alternatives to IFN (Mohamed R, personal communication). Being the main national referral center for liver disease with the highest numbers of hepatologists and gastroenterologists among Malaysia public hospitals, the patients' population in this hospital is likely a good reflection of the affected population treated within tertiary care in Malaysia and the findings in this represent the best available epidemiological data for the country.

In conclusion, this study reveals a relatively high percent liver cirrhosis among HCV-infected patients at initial presentation to a tertiary care center in Malaysia, reflecting delayed referral. The findings also highlights the high number of relatively young patients with cirrhosis at presentation. Data from this study emphasize the importance of timely referral, links to tertiary clinical care centers and the necessity of increasing awareness of HCV infection in the general population. Access to affordable DAA drugs for treatment of hepatitis C within the public healthcare system of Malaysia is essentialif the country is to achieve the WHO elimination target for viral hepatitis by 2030.

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